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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/509,359	07/31/95	ST. GEORGE-HYSLOP	P CAN-004

HM22/0728
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EXAMINER	
BURKE, J	
ART UNIT	**PAPER NUMBER**
1642	37

DATE MAILED: 07/28/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/509,359	George-Hyslop et al
Examiner	**Group Art Unit**
Julie E. Burke, (Reeves), Ph.D.	1642

☒ Responsive to communication(s) filed on *17 May 1999* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *24, 71, 73-77, and 80-94* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *24, 71, 74, 77, 80-86, and 88-94* is/are rejected.

☒ Claim(s) *73, 75, 76, and 87* is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *26, 35*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. The Group and/or Art Unit of U.S. Patent application S.N. 08/509,359 has changed. In order to expedite the correlation of papers with the application please direct all future correspondence to Technology Center 1600, Group 1640, Art Unit 1642.

Continued Prosecution Application

2. The request filed on 5/7/99 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/509,359 is acceptable and a CPA has been established. An action on the CPA follows.

Response to Amendment

3. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

4. Claim 71 has been amended; claims 78-79 have been deleted and claims 80-85 have been added by Amendment D filed 13 Nov 1998. The substitute specification filed 13 Nov 1998 has been entered. Claims 86-94 have been added by the amendment E filed 7 May 1999. Claims 24, 71, 73-77 and 80-94 are pending and under examination.

5. This application is now in compliance with the sequence requirements.

6. The following Office Action contains NEW GROUNDS of rejection.

7. The rejection of claims 24, 71, 74 and 77-79 under 35 U.S.C. 112, first paragraph, is withdrawn in view of the NEW GROUNDS of rejections set forth below.

Applicants' arguments and the Calenda reference cited on Information Disclosure Statement filed 5/7/99 as paper no 35 have been carefully considered but are deemed moot in view of the NEW GROUNDS of rejection set forth below.

8. The following are NEW GROUNDS of rejection.

9. Claims 24, 71, 74 and 77-79 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for E5-1 proteins "comprising" or "consisting of" the sequence of SEQ ID NO:138 (wild type protein) and SEQ ID NO:138 wherein the Asn at amino acid position 141 has been replaced by Ile and/or wherein the Met at amino acid position 239 has been replaced by Val (naturally occurring mutants), does not reasonably provide enablement for other mammalian and human E5-1 proteins, mutations, and splice variants thereof.

a. Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

b. The claims broadly recite any substantially pure human or mammalian E5-1 protein. Other embodiments include any protein with at least one amino acid substitution in SEQ ID NO: 138 or at least one nucleotide mutation in SEQ ID NO: 137. The claims also encompass any naturally occurring mutant of SEQ ID NO: 138, splice variants lacking amino acids 263-296.

c. The specification sets forth a single mammalian species, the wild type human sequence represented by SEQ ID NO:138 and specific mutations thereof.

d. Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al, Journal of Cell Biology Vol 111

November 1990 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (see Lazar et al Molecular and Cellular Biology Mar 1988 Vol 8 No 3 1247-1252).

e. Replacement of the histidine at position 10 of the B-chain of human insulin with aspartic acid converts the molecule into a superagonist with 5 times the activity of nature human insulin. Schwartz et al, Proc Natl Acad Sci USA Vol 84:6408-6411 (1987). Removal of the amino terminal histidine of glucagon substantially decreases the ability of the molecule to bind to its receptor and activate adenylate cyclase. Lin et al Biochemistry USA Vol 14:1559-1563 (1975).

f. These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of the protein. Even if one has the correct amino acid sequence, a skilled practioner would not be able to predict the level of expression of the resulting synthetic DNA sequence For example, the cellular location of the Int-2 oncoprotein is determined by the choice of initiation codon, i.a., either the AUG coding for methionine or CUG coding for leucine. AUG-initiated Int-2 proteins are secreted from the cells, while CUG-initiated Int-2 proteins are localized to the cell nucleus. Acland et al., Nature Vol 343:662-665 (1990).

g. Although biotechnology has made great strides in the recent past, these references serve to demonstrate exactly how little we really know about the art. Elucidation off the genetic code induces one to believe that one can readily obtain a functional synthetic protein for any known nucleic acid sequence with predictable results. The results of the construction of

synthetic proteins remain very unpredictable as Burgess et al, Lazar et al, Schwartz et al, Lin et al and Acland et al conclusively demonstrate.

h. Presence of identical, homologous or similar amino acid residues does not support the conclusion that the proteins have similar functions. As evidenced by Herzog et al, the human homolog of the bovine NPY Y3 receptor contains 92% amino acid identity yet fails to bind NPY or induce any changes with intracellular calcium levels in response to NPY or a number of other ligands (see Abstract, DNA and Cell Biology, Vol 12(6) 465-471 1993). Similarly, Herzog teaches that the IL-8 receptor, angiotensin II receptor and neuropeptide Y receptor contain homologous regions but have has different biological activities. Thus one skilled in the art cannot determine that proteins sharing some identical amino acids would also exhibit similar biological activity absent undue experimentation.

i. One of the main considerations to be made in determining whether undue experimentation is required is the amount of experimentation required. See Ex parte Forman, 230 USPQ 546 (BPAI, 1986). The broad claim language "naturally occurring mutants" or "at least one amino acid substitution", or "at least one mutations", encompasses any and every amino acid being altered in SEQ ID NO: 138, for example. Even if substitutions with the natural 20 amino acids encoded by DNA were the only modifications, instant claims would still broadly encompass a huge number of species;

calculated as 20^N * (length)!/N!/ (length-N)!

wherein "20" is the number of natural amino acids encoded by DNA, "N" is the number of positions where substitutions can occur, "1" is the factorial symbol, "/" is the division symbol and "length" is the total number of amino acids in the protein or peptide. In putting these numbers in perspective, it is noted that the earth is estimated to have existed for 10^{17} seconds (see

Creighton, T.E. 1983. Proteins: Structure and Molecular Principles, W.H. Freeman and Company, NY 93-94, page 94, paragraph 1). There are an estimated 10^{79} atoms in the universe (see page 231 of Creighton, Prog Biophys. Molec. Biol. Vol 33:231-233, 1975). A polypeptide chain of 100 amino acids could exist in 10^{130} combinations and "just one molecule of each of these different proteins would fill the entire [known] universe 10^{27} times over, even if packed together in the most efficient manner" (see paragraph 1, page 94 of 1983 Creighton reference). It is noted that SEQ ID NO: 138 consists of 372 amino acids.

j. The specification fails to identify common identifying characteristics for a substantial portion of the genus, such that one skilled in the art could reasonably predict the general structure of the species within the claimed genus. The specification does not teach how to make and use other proteins with undue experimentation within the broad class of mammalian E5-1 proteins because I) the specification fails to teach that species homologues are indeed present for this specific protein, ii) the specification fails to teach conserved regions of the E5-1 protein which could be used to generate antibodies or develop cloning strategies for the mammalian E5-1 equivalents instantly claimed and iii) since, Alzheimer's is a uniquely human disease, it is not therefore readily apparent that E5-1 species homologues would be present in other mammalian species. Thus, the disclosure of a single species does not enable making the genus.

k. Page 34 lines 3-23, of the specification demonstrates that the human ARMP protein and human E5-1 protein are not encoded by the same gene. Thus, consensus sequences and methodology disclosed at page 34, would not predictably and reproducibly apply to the E5-1 genus. The specification has not demonstrated that equivalent protein E5-1 homologs are present in other mammalian species, present no cloning or protein consensus

sequences for the genus which could predictably and reproducibly identify or species homologues, absent undue experimentation. The specification fails to provide consensus sequences or other guidance so as to guide one skilled in the art to purify other E5-1 species protein homologs. Thus, clearly applicants did not disclose a genus of E5-1 mammalian polypeptides, nor is the specification enabling for making the scope of variants and mutants claimed. Moreover, the specification fails to teach how to use the other mammalian E5-1 proteins, mutants and splice variants. No specific disease has been associated with the E5-1 protein other than Alzheimer's disease. No specific function of the E5-1 protein is set forth in the specification. Thus, even if the skilled artisan could make the E5-1 protein from other mammals, how would these proteins then be used ? While it may be inferred from the specification that antibodies to the naturally occurring proteins (wild type and naturally occurring mutants) may be of use as reagents in a diagnostic assays for Alzheimer's disease. This does not provide a disclosure of how to use other variants, muteins or functionally conserved variants encompassed by the claims. As an extension, since other mammals do not get Alzheimer's disease, how then are these other mammalian proteins to be used ? However, these passages do not teach how to use the other mammalian E5-1 proteins claimed. Because other mammals do not get Alzheimer's disease, these proteins could not be used as diagnostics reagents in other mammals.

I. In view of the breadth of the claims, the inadequate guidance and insufficient examples set forth in the specification, the high level of unpredictability associated with regard to producing and using the myriad of derivatives encompassed in the scope of the claims, as evidenced by the cited art, one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

10. Claims 24, 71, 74, 77 and 80-86, 88-94 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth the isolated E5-1 proteins (1) which consist of or comprise SEQ ID NO: 138 (wildtype); (2) which is encoded by SEQ ID NO: 137 (wildtype); (3) which consist of or comprise SEQ ID NO: 138, wherein the Asn residue at position 141 is substituted by Ile and/or wherein the Met residue at position 239 is substituted by Val (naturally occurring mutants) or (4) which are encoded by SEQ ID NO: 138, wherein the A nucleotide at position 787 is substituted by T nucleotide and/or the A nucleotide at position 1080 is substituted by a G nucleotide (naturally occurring mutants). Therefore the written description is not commensurate in scope with the claims drawn to any purified E5-1 proteins or any naturally occurring proteins or any of the broadly recited mutants.

a. Vas-Cath Inc V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description, inquiry, whatever is now claimed. (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

b. Applicant is reminded that Vas-Cath makes clear that the written description provisions of 35 U.S.C. 112 is severable from its enablement provision (See page 1115). With the exception of the proteins "comprising" or "consisting of", as appropriate, SEQ ID NO: 138 or encoded by SEQ ID NO: 137 or containing the specific point mutations identified above, the skilled artisan cannot envision the detailed structure of the encompassed amino acids and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexicity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The amino acids sequence itself is required. See *Fiers v Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v Chugai Pharmaceutical Co Ltd*, 18 USPQ 1016.

c. Furthermore, in *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by a recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus, At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". Although the instant claims are directed at amino acids and not nucleic acids, the obstacles of isolating amino

acid sequences which are only defined by a function or partial sequence, are similar to those of isolating nucleic acid sequences defined by a function or partial sequence. Therefore, the courts' holdings are applicable to the instant application.

d. Support for the E5-1 protein is provided on page 37, line 11 through page 43, line 15 of the specification. This section, the "Description of the E5-1 Gene" clearly sets forth that, in contrast to the broadly claimed genus, the species E5-1 and the particular isolated mutants are the present invention. No disclosure beyond the mere mention of the broadly encompassed genus is made in the specification. This is insufficient to support the generic claims as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

e. Therefore, only isolated E5-1 proteins (1) which consist of or comprise SEQ ID NO: 138 (wildtype); (2) which is encoded by SEQ ID NO: 137 (wildtype); (3) which consist of or comprise SEQ ID NO: 138, wherein the Asn residue at position 141 is substituted by Ile and/or wherein the Met residue at position 239 is substituted by Val (naturally occurring mutants) or (4) which are encoded by SEQ ID NO: 138, wherein the A nucleotide at position 787 is substituted by T nucleotide and/or the A nucleotide at position 1080 is substituted by a G nucleotide (naturally occurring mutants) meet the written description provision of 35 U.S.C. 112, first paragraph. The specification provides no written description of any other mammalian E5-1 wild type protein, no written description of any mutant of any other mammalian protein.

11. The following are NEW GROUNDS of rejection.

12. Claims 24, 71-72, 74, 77, 80-82, 84, 85-86, 88-94 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 82 is indefinite for reciting "a polynucleotide defined by" because it is not clear whether the claim encompasses proteins encoded by polynucleotides which consist of, comprise or contain portions of SEQ ID NO: 137. If the claim intends to recite proteins encoded by portions of SEQ ID NO: 137, the claim is indefinite because it is not clear which portions of SEQ ID NO: 137 are encompassed in the claims. As written, it is impossible for one skilled in the art to determine the metes and bounds of the claim. Amending the claims to replace the phrase "defined by" with "comprises" or "consists of" would obviate this rejection.

b. Claims 85 and 94 are indefinite for reciting "E5-1 protein encoded by the nucleic acid sequence shown in SEQ ID NO: 137 contains an A>T substitution..." Does the protein or the nucleic acid sequence contain the substitution? Does A stand for alanine or adenosine? If applicant wish the recite that the nucleic acid contains a substitution, then amending the claim to recite "E5-1 protein encoded by the nucleic acid sequence shown in SEQ ID NO: 137, wherein the nucleic acids sequence contains an A>T substitution..." would obviate this rejection.

c. Claims 24, 71, 74, 77, 80-82, 84, 85-86, 88-94 are indefinite for reciting "but having at least one mutation therein" (claim 88, for example) because (1) it is not clear how many mutations are encompassed by the claims (can every amino acid be altered? Would the protein still be an "E5-1" protein if every amino acid is changed?). The claims are further indefinite because it

is not clear whether the limitation which begins with the term "but" is a positive or negative limitation.

d. Claims 24, 71, 74, 77, 80-82, 84, 85-86, 88-94 are indefinite for reciting the laboratory designation "E5-1", absent any identifying structural or functional characteristics, as unique depository information to distinguish the claimed proteins from any other protein which may be designated with the similar label. Other laboratories/inventors may use the same laboratory designation to refer to different proteins.

Claim Objections

13. Claims 73, 75, 76 and 87 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Status of Claims

14. Claims 24, 71, 74, 77 and 80-86, 88-94 are remain rejected.

Conclusion

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie E. Burke, née Reeves, Ph.D, whose telephone number is (703) 308-7553. The examiner can normally be reached on Monday through Friday from 8:00 am to 5:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308-4310. Any inquiry of a

general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

16. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Respectfully,

Julie C Burke

Julie E. Burke, née Reeves, Ph.D.

Primary Patent Examiner

(703) 308-7553

JULIE BURKE
PRIMARY EXAMINER